BUPRENORPHINE HYDROCHLORIDE: DETERMINATION OF ANALGESIC POTENCY

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BUPRENORPHINE HYDROCHLORIDE was synthesized in 1966 in the laboratories of Reckitt and Colman in Britain. It is an N-cyclopropylmethyl oripavine and thebaine derivative with a more complex structure than morphine (Figure 1).

FIGURE 1

In animal tests it was found to have an analgesic effect that is at least 35 times more potent than morphine and about half as potent as fentanyl (Sublimaze). It has, also, a morphine antagonistic effect that is approximately three times stronger, with a duration of action six times longer, than naloxone (Narcan). The only frequently seen side-effect is drowsiness.

Between 1973 and 1975 this compound was shown by Lewis and associates to have substantial advantages over morphine and related potent analgesics in animals. Its depressant action on respiration was very weak; the onset of analgesia appeared to be more rapid and the duration of analgesia much longer than with morphine; its addiction propensity was extremely weak, and it had a high therapeutic index.¹ In initial tests, clinicians²⁻⁴ have observed in man that drowsiness is the only common side-effect, regardless of the route of administration. If respiratory depression occurred with a large intramuscular dose, that response was effectively reversed by naloxone (Narcan).⁵

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TABLE I
BUPRENORPHINE HCl - ANALGESIC EFFECT

Dose	Sex		Race		Mean age	Mean weight (kg)	Mean height (cm)	Total
	male	female	Caucasian	Non-Caucasian				
0.1 mg	2	9	10	1	52	60	165	11
0.2 mg	3	7	9	1	44	64	165	10
0.3 mg	7	12	18	1	40	63	163	19
0.4 mg	3	15	15	3	39	79	164	18
0.5 mg	1	4	5	0	29	80	166	5
0.6 mg	2	0	2	0	23	87	176	2

This project was undertaken to determine, in a single dose intramuscular study, an effective dose range of buprenorphine hydrochloride in patients with severe pain following a major surgical procedure.

Virtually all patients in this study were premedicated with diazepam and atropine; anaesthesia was induced with thiopentone and managed with enflurane, nitrous oxide and pancuronium. Residual effect of the relaxant was reversed with atropine and prostigmine at the end of the operation.

METHODS

The design of this single dose study was open-label and non-randomized. First, four groups of at least 10 post-operative patients, who were awake in the recovery room and complaining of severe pain, each received a single dose of buprenorphine hydrochloride (0.4 mg/ml) by intramuscular injection in the deltoid region of the arm. The first group received buprenorphine 0.1 mg (0.25 ml). This dose was well tolerated. A second group received buprenorphine 0.2 mg (0.50 ml). Good tolerance was observed at this dose level also. The third and fourth groups received 0.3 mg (0.75 ml) and 0.4 mg (1.00 ml). Both these groups had satisfactory analgesia, often accompanied by drowsiness. Some patients received a dose of 0.5 mg (1.25 ml) and 0.6 mg (1.5 ml). The total number of patients in each dose level is shown in Table I.

Immediately prior to, and at $\frac{1}{2}$, 1, 2, 3, 4, 5 and 6 hours after the administration of buprenorphine the following measurements were recorded: (a) pain intensity: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe; (b) pain relief (no score at baseline): 0 = none, 1 = slight, 2 = moderate, 3 = good, 4 = complete; (c) degree of sedation: 1 = alert, 2 = mildly drowsy, 3 = moderately drowsy; 4 = asleep; (d) respiratory rate; (e) pulse rate (lying); (f) auscultatory blood pressure (lying). These vital signs were also recorded pre-operatively. All patients in this study were kept under direct surveillance for a minimum of eight hours and were seen again the next day for follow-up. Pain scoring was discontinued for those patients who required additional analgesic medication before the end of the 6-hour test period. Most such occurrences were among the patients who received less than 0.3 mg buprenorphine hydrochloride.

Statistical Analyses

The dose groups were analyzed for comparability of age, weight and height distributions, using analyses of variance. In the analysis of weight and height, the model also included the blocking effect due to sex.

Although the assignment of patients to a dose level was not randomized, we expected that the severity of pain at baseline would be comparable in the dose groups to allow for the comparison of the responses. To determine this, the hypothesis of equality of mean pre-drug pain intensity scores was tested using a one-way analysis of variance. Rejection of the hypothesis would alter further evaluation of the study since the dose groups were studied sequentially.

Two over-all measures of the change in the pain intensity were derived from the raw pain scores. To form these measures for each post-drug observation time, the differences between the pre-drug and post-drug pain intensity scores (denoted PID) were calculated first. The next step was to compute the summations through three and six hours of the products of each PID and the corresponding time interval since the previous observation. The average pain reduction over the first three and six hours (AVPRED 3 and AVPRED 6) were then computed by dividing these summations by three and six hours, respectively.

In like manner, two corresponding overall measures of the pain relief were derived from the raw pain relief scores. The summations through three and six hours of the products of each pain relief score, and the corresponding time interval since last observation, were calculated first. The average pain relief over three and six hours (AVPREL 3 and AVPREL 6) was then computed by dividing these summations by three and six hours, respectively.

Pain relief scores of patients who received additional medication before completion of the 6-hour test period were 0 (no relief). The observed scores plus those assigned were used in the calculation of the AVPRED and AVPREL values.⁶

The AVPRED 3's and AVPREL 3's multiplied by three hours are actually the sum of pain intensity differences ("SPID") and total pain relief score ("TOTPAR") values (through three hours), which are often seen in the literature.⁶ Similarly, the AVPRED 6 and AVPREL 6, multiplied by six hours, equal the SPID and TOTPAR values (through six hours). The AVPRED and AVPREL parameters represent the average pain reduction and pain relief (weighted for unequal observation intervals), and provide a better understanding of the results than do the SPID and TOTPAR parameter, which are merely totals. For example, an AVPREL 3 score of 3 would indicate that the patient received "good" pain relief during the first three hours, but a TOTPAR score of 9 does not elicit as clear a picture. It should be pointed out, however, that the results are the same using AVPREL's or TOTPAR's or, similarly, AVPRED's or SPID's.

For each of the four parameters, the six-dose levels were compared using analysis of variance. The model included effects due to pre-drug pain intensity (a blocking factor) and dose. The effect of the pre-drug pain intensity was fitted in the model before determining the effect of dose.⁷ The mean response for each dose was adjusted for the differences in the pre-drug pain intensity. Pair-wise comparison was performed on the adjusted means, using a t-test (two-sided). The standard error of the difference between the two adjusted means was computed using the appropriate elements of the $(X'X)$ inverse matrix.

TABLE II
BUPRENORPHINE HCl - ANALGESIC EFFECT

Dose (mg)	No. of patients	Mean Pain Intensity Scores*							
		Hours							
		0	$\frac{1}{2}$	1	2	3	4	5	6
0.1	11	3.1	2.2	1.7	2.0	2.2	2.4	2.7	2.7
0.2	10	3.0	2.0	1.8	2.1	2.0	2.1	2.1	2.3
0.3	19	2.9	2.0	1.5	1.5	1.5	1.6	1.9	2.1
0.4	18	3.1	2.2	1.6	1.2	1.4	1.8	2.2	2.4
0.5	5	3.0	1.8	1.4	1.0	1.6	1.8	2.0	2.6
0.6	2	3.5	2.0	0.5	0.5	1.0	1.5	1.5	1.5

Dose (mg)	No. of patients	Mean Pain Relief Scores*							
		Hours							
		$\frac{1}{2}$	1	2	3	4	5	6	
0.1	11	1.1	1.7	1.7	1.5	1.1	0.5	0.5	
0.2	10	0.9	1.6	1.5	1.5	1.3	1.2	1.0	
0.3	19	1.5	2.1	2.4	2.3	2.1	1.7	1.3	
0.4	18	1.5	2.3	2.7	2.6	1.9	1.4	1.0	
0.5	5	1.6	2.2	2.8	2.2	1.8	1.6	0.8	
0.6	2	1.5	3.0	3.5	2.5	2.0	2.0	2.0	

*Note that the means are computed using both the observed and assigned scores.

RESULTS

1. Demographic variables (see Table I)

The dose groups had comparable sex distributions. Over-all, 47 of the 65 patients were female. All but six patients were Caucasian and the dose groups appeared comparable with respect to race.

The mean ages of the dose groups were found to differ significantly. The mean age appeared to be lowest for the higher doses, i.e., the mean age decreases from a high of 52 years in the 0.1 mg dose group to a low of 23 years in the 0.6 mg dose group. The dose groups also appeared to be significant with respect to weight. Generally, the mean weight was higher for the larger doses. The average weight ranged from 60 to 64 kg in the 0.1 mg, 0.2 mg and 0.3 mg dose groups, to 79 to 87 kg in the 0.4 mg, 0.5 mg and 0.6 mg dose groups. The mean heights of the dose groups were comparable - the over-all average being 165 cm.

The age and weight differences between the dose groups have been ignored, since the differences are small compared to the dose range studied. Also, the effects of these differences are probably small when compared to the effect of the initial pain intensity.

2. Pain severity of dose groups at baseline (Table II)

The dose groups appeared comparable with respect to the pain intensity at baseline, as no differences between dose groups were detected. Over-all, at baseline, three patients had moderate pain, 56 patients had severe pain, and six had very severe pain. The average baseline pain intensity of all six-dose groups was 3.0 (severe pain).

FIGURE 2

3. Efficacy

The mean Pain Intensity and mean Pain Relief scores at each observation time are presented in Table II. Note that the scores assigned to missing values (see Statistical Analyses above) were included in the calculation of these means. Plots of each Pain Intensity and Pain Relief means, over time, are presented in Figures 2 and 3, respectively. From the graphs, a sharp reduction in pain intensity and corresponding increase in pain relief are evident by the one-half hour observation. The peak pain relief appears to occur between one and two hours. The analgesic activity appears to be sustained for three to four hours before diminishing but, even at six hours, activity appears to be measured – as mean pain relief is still greater than slight, in most of the dose groups.

The raw and adjusted AVPRED and AVPREL means are presented in Table III.

The average pain reduction over three hours (AVPRED 3)

There was a significant difference ($P < 0.05$) among the dose level means when they were fitted sequentially after fitting the blocking factor (baseline pain severity). The pair-wise comparisons showed that the 0.6 mg dose (adjusted mean = 2.5) was significantly more efficacious than either the 0.1, 0.2 or 0.3 mg doses (adjusted means = 1.0, 0.9 and 1.3, respectively). The 0.4 mg dose (adjusted mean = 1.6) had significantly greater pain reduction than the 0.2 mg dose. A statistically significant trend, in which the 0.4 mg dose was favored over the 0.1

FIGURE 3

mg dose, was also seen. The 0.5 mg dose (mean = 1.5) appeared comparable to the 0.4 mg dose.

The average pain relief over three hours (AVPREL 3)

The dose level means were significantly different when they were fitted sequentially after fitting the blocking variable (baseline pain severity). The higher dose levels provided more pain relief than the lower doses. The 0.1 and 0.2 mg doses with adjusted means of 1.7 and 1.5, respectively, appeared comparable. The 0.3, 0.4 and 0.5 mg dose levels (adjusted means = 2.2, 2.5 and 2.4) had approximately the same pain relief, which was less than that of the 0.6 mg dose level (3.2). The 0.3, 0.4, 0.5 and 0.6 mg dose levels achieved greater than moderate pain relief (a score of 2) over the first 3 hours. The pair-wise comparisons showed significantly greater relief for the 0.4 and 0.6 mg dose levels than for either the 0.1 or 0.2 mg dose levels. The pain relief for the 0.3 and 0.5 mg doses was greater than that of the 0.2 mg dose.

The average pain reduction over six hours (AVPRED 6)

After fitting the pre-drug pain intensity blocking factor, the means of the six-dose levels were not found to be significantly different. The pair-wise comparisons between the 0.6 mg dose and either the 0.1 mg and 0.2 mg dose levels were significant with the 0.6 mg dose (adjusted mean = 2.3) providing greater pain

TABLE III
BUPRENORPHINE HCl - ANALGESIC EFFECT

No. of patients	Dose	MEANS			
		AVPRED 3	AVPRED 6	AVPREL 3	AVPREL 6
11	0.10	1.0	0.8	1.6	1.1
10	0.20	1.0	0.9	1.4	1.3
19	0.30	1.4	1.2	2.2	1.9
18	0.40	1.6	1.3	2.4	1.9
5	0.50	1.6	1.2	2.3	1.9
2	0.60	2.6	2.3	2.8	2.4
Means adjusted for pain before medication (Time zero)					
No. of patients	Dose	AVPRED 3	AVPRED 6	AVPREL 3	AVPREL 6
11	0.10	1.0	0.7	1.7	1.2
10	0.20	0.9	0.8	1.5	1.2
19	0.30	1.3	1.1	2.2	1.8
18	0.40	1.6	1.2	2.5	1.9
5	0.50	1.5	1.1	2.4	1.8
2	0.60	2.5	2.3	3.2	2.6

reduction over six hours than either the 0.1 mg or 0.2 mg doses (means = 0.7 and 0.8). The 0.3, 0.4 and 0.5 mg dose levels (adjusted means = 1.1, 1.2, and 1.1, respectively) reduced the pain intensity from severe to an average of moderate over the 6 hours.

Examination of the AVPRED 3 and AVPRED 6 means indicates less pain reduction for the latter parameter. This is understandable because after three hours the effect of the drug begins to diminish and the AVPRED 6 is the average over the entire six-hour observation period. The analgesic effect could also wear off at different rates because of individual differences, thus increasing the overall variability of the system and reducing the ability of the statistical test to detect true differences between the dose levels. A greater mean squared error for the AVPRED 3 indicates greater variability over six hours than over three hours. Nevertheless, it should be noted that the AVPRED 3 and AVPRED 6 means both show the same general pattern - greater efficacy for the 0.3-0.6 mg doses than for the 0.1 or 0.2 mg doses.

The average pain relief over six hours (AVPREL 6)

The mean of the six doses were not found to be significantly different when they were fitted sequentially after fitting the blocking factor (initial pain intensity). Although the dose levels were not significantly different, the average pain relief did increase with increasing dose. The 0.1 and 0.2 mg doses showed approximately slight relief over the six-hour period while the 0.3, 0.4 and 0.5 mg doses showed moderate relief. The 0.6 mg dose (only two patients) showed good relief for the six hours.

The mean squared error of the AVPREL 6 is greater than that of the AVPREL 3. The means for both the AVPREL 3 and AVPREL 6 show the same pattern of greater efficacy for the 0.3-0.6 mg doses than for the 0.1 and 0.2 mg dose levels.

Side-effects

Drowsiness was by far the commonest side-effect observed and was seen in approximately 40 per cent of the patients who received 0.3 mg or more of buprenorphine hydrochloride. In these patients, there was usually a slowing of the pulse rate. Respiratory rate did not change appreciably nor was there significant reduction in the tidal volume or blood pressure. Miosis was observed in a few patients at all dose levels. Aside from varying degrees of pain relief at 0.2 mg and the lower dose, drowsiness was seen infrequently. Nausea and vomiting occurred in the recovery room in five patients who received buprenorphine hydrochloride. Some of these side-effects were undoubtedly due to other factors.

On the basis of this open study, it was observed that approximately 0.3 mg buprenorphine hydrochloride was satisfactory analgesic for severe pain, without the occurrence of disturbances in vital signs or significant side-effects.

SUMMARY AND CONCLUSIONS

An open evaluation of relief from severe pain following major abdominal operations was carried out on at least ten patients, who had given written consent, with 0.1 to 0.4 mg doses of buprenorphine hydrochloride administered intramuscularly. Statistical analysis of the data showed that 0.3 mg of this compound provided quite satisfactory relief from pain for up to six hours. Seven more consenting patients were given buprenorphine hydrochloride 0.5 to 0.6 mg, but they did not receive much greater or longer pain relief than those receiving 0.3 to 0.4 mg. However, the latter patients were younger and heavier. It was concluded that buprenorphine hydrochloride 0.2 to 0.4 mg provided relief of severe pain probably as well as is observed with morphine 10 mg for the average-size patient, but the duration of pain relief with the new compound is substantially longer than with other strong analgesics previously tested. The only common side effect noted was drowsiness, which was observed during the analgesic action of the compound. No appreciable alterations were seen in the respiration, pulse rate and blood pressure.

On the basis of these tests, buprenorphine hydrochloride appears to be a satisfactory analgesic for severe postoperative pain, and it deserves extensive study.

RÉSUMÉ

Cette étude porte sur l'analgésie obtenue en post-opératoire immédiate, chez des patients ayant subi une chirurgie abdominale majeure.

Les patients furent divisés en quatre groupes (non standardisés), d'au moins 10 malades chacun, et chaque groupe reçut une dose différente d'hydrochlorure de buprenorphine intramusculaire (de 0.1 à 0.4 mg).

L'analyse des résultats a démontré qu'une dose de 0.3 mg du médicament procurait une analgésie satisfaisante, dont la durée allait jusqu'à six heures.

Sept autres patients ont accepté de recevoir une dose de 0.5 ou 0.6 mg. Dans ces cas, on a constaté peu de différence entre eux et les groupes ayant reçu 0.3-0.4

mg (quant à l'intensité de la durée d'action du médicament). Notons cependant que ces sept malades étaient plus jeunes et plus corpulents que la moyenne.

Nous avons conclu que, pour le patient de taille moyenne, 0.2 à 0.4 mg d'hydrochlorure de buprenorphine assurait un soulagement comparable à 10 mg de Morphine. Par contre, la durée d'action de l'analgésie était plus longue.

Le seul effet secondaire notable fut un assoupissement rencontré durant la période d'analgésie. On n'a par ailleurs pas enregistré de modifications significatives de la respiration, du pouls et de la tension artérielle.

Se basant sur cette étude, nous croyons que le buprenorphine est un analgésique efficace pour soulager une douleur post-opératoire intense et qu'à ce titre, il mérite une étude plus poussée.

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